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Attorneys for Isis Pharmaceuticals, Inc.

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE SOUTHERN DISTRICT OF CALIFORNIA

SAN DIEGO DIVISION

ISIS PHARMACEUTICALS, INC., a Delaware Corporation,

Plaintiff,

v.

SANTARIS PHARMA A/S CORP., a Delaware corporation, and SANTARIS PHARMA A/S, a Danish Corporation,

Defendants.

Case No. 11-CV-02214 GPC (KSC)

FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

DEMAND FOR JURY TRIAL

Plaintiff Isis Pharmaceuticals, Inc., complains against Defendants Santaris Pharma A/S Corp. and Santaris Pharma A/S (collectively "Santaris") as follows:

THE PARTIES

1. Plaintiff Isis Pharmaceuticals, Inc. ("Isis"), is a corporation organized under the laws of Delaware, having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010.

2. On information and belief, Defendant Santaris Pharma A/S Corp. is a privately held company, incorporated in the State of Delaware, having a principal place of business at 12626 High Bluff Drive, Suite 440, San Diego, California 92130. On information and belief, Santaris Pharma A/S Corp. is registered to do business in the State of California. On information and belief, and as further explained below, Santaris Pharma A/S Corp., itself and as the agent and wholly owned subsidiary of Santaris Pharma A/S, is in the business of discovering and commercializing RNA-targeted therapies through third parties in the State of California and throughout the United States.

3. On information and belief, Santaris Pharma A/S is a privately held biopharmaceutical company organized and existing under the laws of Denmark, having a principal place of business at Kogle Allé 6, DK-2970 Hørsholm, Denmark. On information and belief, and as further explained below, Santaris Pharma A/S, itself and through its wholly owned subsidiary and agent, Santaris Pharma A/S Corp., is in the business of discovering and commercializing RNA-targeted therapies through third parties in the State of California and throughout the United States. Santaris Pharma A/S Corp. is the alter ego of Santaris Pharma A/S, where a unity of interest and ownership exists between Santaris Pharma A/S and Santaris Pharma A/S Corp, such that separate personalities of the two do not in reality exist. Isis is informed and believes, and on that basis alleges, that Defendants were at all times relevant the partners, officers, agents, assignees, successors-in-interest, co-conspirators, principals, alter egos, or employees of each other, or were otherwise responsible for, contributed to, or participated in the acts and omissions alleged herein, and thereby incurred liability therefore.

JURISDICTION AND VENUE

4. This is an action for patent infringement arising under the patent laws of the United States (Title 35 of the United States Code) and arising from Santaris's sale, offer to sell, use or importation of Isis's patented methods and/or compositions prior to the expiration of U.S. Patent Nos. 6,326,199, 6,066,500, and 6,440,739. The Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a) and Section 2201.

5. This Court has personal jurisdiction over Santaris by virtue of the fact that Santaris conducts business in the State of California, and has availed itself of the rights and benefits under California law, and has engaged in substantial and continuous contacts in the State of California.

6. To the extent that Santaris Pharma A/S (Denmark) successfully contends that it is not doing business in California, personal jurisdiction over Santaris Pharma A/S is proper under Federal Rule of Civil Procedure 4(k)(2).

7. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and 1400.

THE PATENTS-IN-SUIT

8. On December 4, 2001, United States Patent No. 6,326,199 (the "'199 Patent") entitled "Gapped 2' Modified Oligonucleotides" issued to Isis Pharmaceuticals, Inc., as assignee of the inventors. (A copy of the '199 Patent is attached as Exhibit 1.)

9. On May 23, 2000, United States Patent No. 6,066,500 (the "'500 Patent") entitled "Antisense Modulation of Beta Catenin Expression" issued to Isis Pharmaceuticals, Inc., as assignee of the inventors. (A copy of the '500 Patent is attached as Exhibit 2.)

10. On August 27, 2002, United States Patent No. 6,440,739 (the "'739 Patent") entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression" issued to Isis Pharmaceuticals, Inc., as assignee of the inventors. (A copy of the '739 Patent is attached as Exhibit 3.)

11. The '199, '500 and '739 Patents (collectively the "patents-in-suit") have been owned by Isis at all times, are fully maintained, and are valid and enforceable.

DRUG DISCOVERY AND DEVELOPMENT

12. In the fields of medicine and biotechnology, drug discovery is the process by which drugs are designed and/or identified. The process of drug discovery involves target validation and drug candidate identification. During the target validation phase, pharmaceutical researchers test a hypothesis that, for example, the reduction of a given protein target will yield a biochemical change potentially relevant for treating disease. Candidate identification commences after a target has been validated in relevant disease models and often involves screening numbers of compounds for their biological activity. Once a compound has been identified through the foregoing process and shown to have the specific desired activity, it will enter the process of drug development.

13. Drug development refers to activities undertaken after a compound has been identified as a potential drug that seek to establish its suitability as a medication. This process determines appropriate formulation and dosing, as well as establishes safety. Research in these areas generally includes a number of required *in vivo* studies and clinical trials in healthy volunteers to assess safety, and ultimately in patients to assess therapeutic value as a medication. Certain pre-clinical and clinical data generated during the drug discovery phase may ultimately form the basis for a filing with the Food and Drug Administration (FDA) for regulatory approval to market the drug in the United States.

ANTISENSE TECHNOLOGY

14. Proteins are fundamental components of all living cells, and include many types of molecules necessary for carrying out cellular functions. The overproduction or abnormal production of proteins is implicated or associated with many diseases. Genes are DNA chemical entities within the nuclei of cells that hold the information necessary to make proteins. This information is converted into proteins in two steps called transcription and translation. At the transcription step, the genetic information for a given protein is copied to a molecule called messenger RNA (mRNA). During translation, cellular machinery converts the information embodied in the mRNA into proteins.

15. Most drugs produced by the pharmaceutical and biotechnology industries, such as small molecules (*e.g.*, Lipitor) or monoclonal antibodies (*e.g.*, Enbrel) are designed to bind to and interfere with the function of disease-causing proteins. Antisense technology differs from those pharmaceutical approaches. Antisense compounds target specific mRNAs that encode disease-causing proteins. Thus, antisense works by preventing or reducing protein production altogether, rather than interfering with protein function after it is produced. This mechanism presents another way to treat and potentially cure disease. Antisense technology has several additional advantages over traditional drugs, including the ability to modulate proteins that are not amenable to small molecule drugs. It can also be used in basic research to better understand the function of target proteins. For example, a researcher can use antisense in cells to reduce the production of a protein of unknown function and observe the consequences. One may use normal cells or cells from patients of a particular disease.

16. An antisense compound is typically a short, single-stranded DNA polymer, often called an "oligonucleotide," that is comprised of individual units called nucleotides.[1] These oligonucleotides can be modified to alter their natural properties – a concept that lies at the heart of Isis's inventions. These oligonucleotides are designed to bind by hybridization to a specific mRNA transcript (the "sense" strand) that encodes a target protein to form a duplex. A cellular enzyme, called RNase H, recognizes that duplex and causes degradation of the mRNA, thereby preventing synthesis of the target protein. By inhibiting the production of proteins involved in disease, antisense drugs can thus create therapeutic benefits for patients.

ISIS AND ITS BUSINESS OF ANTISENSE DRUG DISCOVERY

17. Isis is the global leader in antisense drug discovery and development, with a broad pipeline of 24 drugs in development and several others in early stage research targeted to many proteins associated with different diseases. Isis has expanded the reach of antisense drugs by

[1] An oligonucleotide is chemically synthesized and has a length that typically spans 10-50 nucleotides. Nucleotide units are themselves comprised of three components: (i) a nitrogen-containing ring structure known as a "base", (ii) a pentofuranosyl sugar moiety, and (iii) a phosphate-containing linker. Any of these components can be chemically modified to alter an oligonucleotide's natural properties.

addressing a wide range of diseases such as cancer, diabetes, cardiovascular disease, neurodegenerative disease and other diseases of genetic origin. Isis was founded in 1989 by antisense pioneer Stanley Crooke, M.D., Ph.D., and his colleagues. To this day, Dr. Crooke serves as Isis's Chief Executive Officer and actively leads a group of researchers looking to understand more fundamentally how antisense drugs work and how to further optimize them. Isis is a Carlsbad, California-based company that employs nearly 350 people.

18. Since Isis's inception, the company has focused on studying how antisense works and translating this new knowledge to optimize antisense drug designs and methods of drug discovery. During its twenty-two year history, Isis has made enormous investments of time, money and effort to develop platform antisense technology.[2] This antisense drug design platform technology allows Isis scientists to identify protein targets of interest, and to create potent chemically-modified antisense compounds that can inhibit virtually any specific protein of therapeutic importance.

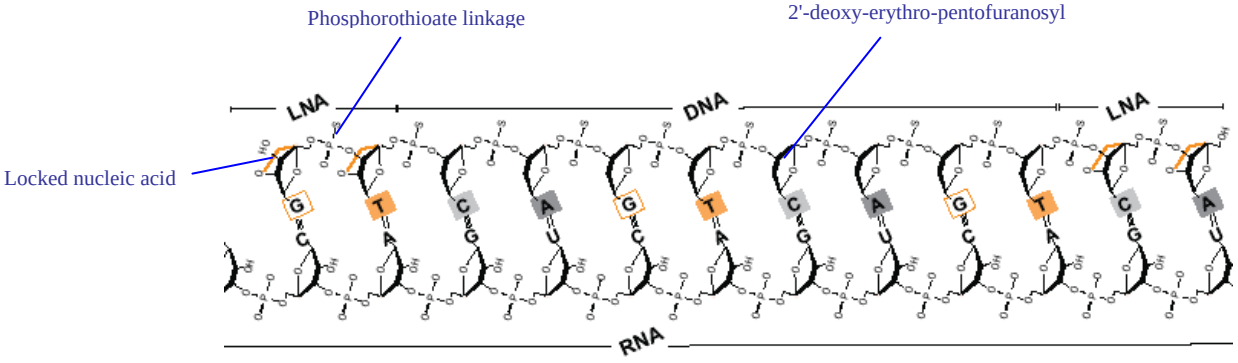
19. Isis maintains its focus on further research and development of antisense compounds and technology, rather than on late-stage drug development and commercialization. Isis has developed a business model in which it partners with and relies on other pharmaceutical companies to develop further the antisense drugs that Isis identifies in the drug discovery phase using Isis's platform antisense technology. Isis's pharmaceutical company partners typically perform drug development and clinical trials, seek final market approval, and ultimately commercialize the purchased antisense drug candidates. This business strategy enables Isis to earn upfront fees, milestone payments, and royalties as Isis's partners further develop the antisense drugs based on the drug discovery research performed by Isis. Since 2007, Isis's partnerships generated more than $840 million in payments from fees, milestones, equity investment, and research and development funding.

[2] "Platform antisense technology" generally refers to features of antisense compound design that can be incorporated into any antisense compound, independent of the specific protein targeted or the base sequence of the mRNA encoding it. Platform technology enables the owner of the platform to more rapidly and cost-efficiently produce a series of products incorporating the technology because some basic research does not need to be performed for each new product.

ISIS'S PATENTED ANTISENSE DRUG DESIGN PLATFORM TECHNOLOGY

20. One of Isis's earliest and most transformative platform technologies is the invention of "gapmer" or "gapped" oligonucleotide compounds for uses in a cell as embodied in the method claims of the '199 Patent. Like all antisense compounds, "gapmers" comprise linked nucleotides (oligonucleotides) and have a base sequence that specifically hybridizes to the complementary sense strand of a target mRNA to disrupt the production of the resulting protein. Gapmers further comprise modifications arranged along the oligonucleotide to protect it from degradation by cellular nucleases and to increase binding affinity of the oligonucleotide to its target; and a plurality of unmodified 2'-deoxy-erythro-pentofuranosyl sugar moieties which elicit degradation of the mRNA. Such antisense compounds are particularly suited for reducing the amount of target protein in a cell and, therefore, are useful for identifying targets of therapeutic value and for identifying potential drug candidates.

21. An example of a gapmer oligonucleotide used in Isis's patented methods is found in Santaris's 2010 Annual Report, a relevant section of which is reproduced below:



22. The above oligonucleotide is functionalized to increase nuclease resistance. Specifically, it employs phosphorothioate linkages, to increase stability of the oligonucleotide in the presence of nucleases, which degrade oligonucleotides lacking such modifications. The oligonucleotide also comprises modified bicyclic ribose sugar rings, called locked nucleic acid ("LNA"), which is substituted at the 2' position of the ribose ring with an oxy-methylene bridge that is covalently bonded to the 4' position of the ribose ring. The LNA modification increases the binding affinity of the oligonucleotide to its complementary strand. Finally, the middle of the oligonucleotide comprises a plurality of nucleotides that comprise 2'-deoxy-erythro-

pentofuranosyl sugar moieties. This portion of the gapmer serves to attract RNase H, which in turn causes degradation of the mRNA, and thereby prevents the production of the target protein. The above oligonucleotide is contacted with a cell to inhibit the production of a protein.

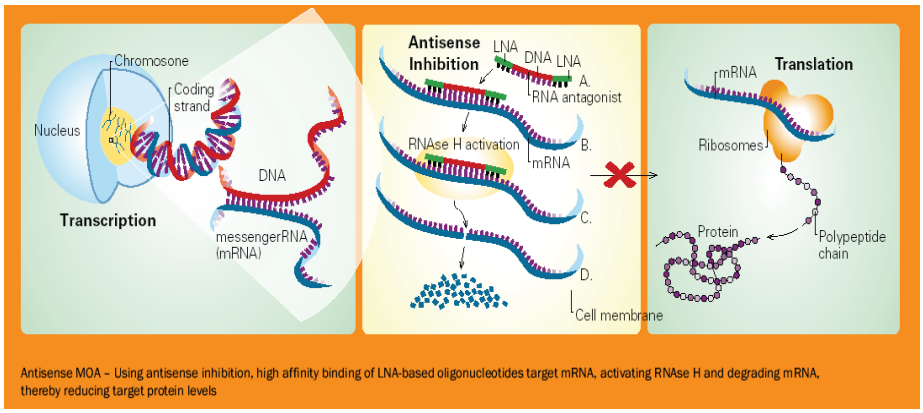
23. Isis has also designed, evaluated, and developed candidate antisense compounds incorporating its platform technology as applied to certain targets for specific disease indications. One such invention was conceived at Isis by Drs. C. Frank Bennett and Lex M. Cowsert. This invention directs antisense compounds at the overproduction of a protein called "beta-catenin," which has been shown to promote development of several types of cancers, including those affecting the colon and skin. Antisense oligonucleotides that hybridize to beta-catenin mRNA, and thereby cause the destruction of this genetic message, decrease the production of beta-catenin protein in cancer cells, and may ultimately provide a therapeutic benefit to patients. Isis developed several antisense compounds directed to beta-catenin and garnered patent protection for these inventions through the '500 Patent. The '500 Patent also claims a method for practicing Isis's beta-catenin inhibition process that comprises contacting cells or tissues in a laboratory dish with antisense compounds that reduce beta-catenin protein production. The antisense compounds claimed in the '500 Patent are not required to be gapmers.

24. Another patent directed to antisense compositions and methods that modulate the production of a protein is Isis's '739 Patent, directed to the expression of glioma-associated oncogene-2. Over expression of glioma-associated oncogene-2 is associated with a number of human developmental syndromes and cancers. Antisense oligonucleotides that hybridize to the glioma-associated oncogene-2 mRNA, and thereby cause the destruction of this genetic message, decrease the production of glioma-associated oncogene-2 protein in cancer cells, and may ultimately provide a therapeutic benefit to patients. Isis developed several antisense compounds directed to glioma-associated oncogene-2 and garnered patent protection for these inventions through the '739 Patent. The '739 Patent also claims a method for practicing Isis's glioma-associated oncogene-2 inhibition process that comprises contacting cells or tissues in a laboratory dish with antisense compounds that reduce glioma-associated oncogene-2 protein production. The antisense compounds claimed in the '739 Patent are not required to be gapmers.

INFRINGING ACTS BY SANTARIS

25. Santaris engages in the business of selling antisense drug discovery services and products to pharmaceutical company customers in the United States. These activities are in direct competition with Isis. Santaris was founded to discover and commercialize gapmers that comprise locked nucleic acid nucleotides. As discussed above, a locked nucleic acid is a modified nucleotide in which a hydroxyl group at the 2' position of a ribose ring has been substituted with an oxy-methylene bridge that is covalently bound to the 4' position of the ring. Gapmers, also discussed above, are antisense compounds having a specific arrangement of functional modifications, as described and claimed in the '199 Patent.

26. On information and belief, Santaris uses the LNA-containing gapmer antisense compounds in cell assays to assist with the identification of potential gene targets and/or to screen the ability of synthesized oligonucleotides to inhibit the production of a specific protein. The Santaris 2010 Annual Report confirms these activities and uses:



Thus, the Isis method patented in the '199 Patent, which involves contacting a cell with a gapmer, is used by Santaris as a research tool to identify targets and/or to screen gapmer LNA antisense molecules for activity inhibiting a target. Santaris further sells and offers for sale in the United States the patented methods of the '199 Patent. Santaris's business has been built around exploiting the platform antisense technology pioneered and patented by Isis, and selling and offering it for sale to pharmaceutical companies.

27. On information and belief, at least some of Santaris's sales are memorialized in commercial agreements with its pharmaceutical company customers, pursuant to which Santaris agreed to transfer property and/or perform services for a certain price. On information and belief, these agreements typically involve Santaris performing some combination of the following activities in exchange for cash consideration: (1) assays using gapmer antisense compounds for the discovery and/or identification of possible protein targets, (2) validation experiments designed to determine whether inhibition of target protein is therapeutically relevant, (3) synthesis and testing of a number of gapmer antisense compounds (typically hundreds or thousands) to screen for effectiveness in reducing target protein, and (4) transfer of gapmer-based antisense technology and compounds to the customer for further validation and development. These commercial sales or offers for sale compete with the '199 Patent drug discovery services Isis sells or offers for sale in the United States.

28. On information and belief, Santaris has attempted to compete directly with Isis by advancing and selling LNA gapmer compounds for a specific mRNA target for which Isis has already invested research time and money to validate as a viable therapeutic target for antisense. Specifically, Santaris has offered for sale and sold to Enzon Pharmaceuticals, Inc., antisense compounds that inhibit beta-catenin and glioma-associated oncogene-2 production in violation of the '500 Patent and the '739 Patent, respectively.

29. On information and belief, Santaris has further induced the infringement of the '199 Patent. Santaris has had knowledge of the patent at least prior to 2006. Indeed, Santaris unsuccessfully challenged Isis's European Patent that stemmed from the original patent application filed in the United States by the inventors of the '199 Patent and is directed to similar patented subject matter. Further, Santaris has licensed and provided to its pharmaceutical company partners know how associated with the contacting of an LNA molecule with a cell *in vitro* to screen for the activity of the supplied LNA molecules and/or to further validate a gene target. Under the terms of the agreements with certain of the pharmaceutical partners, Santaris supplied that know how and materials to the pharmaceutical company partners intending that they use such materials and know how to contact an LNA compound with the cell in such a manner

that performs in the United States each step of the methods claimed in the '199 Patent by the pharmaceutical partners and/or their collaborators. At the time of providing such materials and know how for screening or target validation purposes, Santaris knew that the acts of its pharmaceutical partners and/or collaborators would constitute infringement of the '199 Patent. Examples of nonpublic documents recently produced by Santaris that show such inducing activity may be found at SANAS00007725-29; SANAS00007921; SANAS0000239; SANAS0000185; SANAS00012056-84; SANAS00012407-410; SANAS00010598; SANAS00011827 at pp. 39-42; SANAS00012607; SANAS00021473; SANAS00023623; SANAS00117937.

30. On information and belief, Santaris has performed infringing acts in the United States using the methods of the '199 Patent to demonstrate to potential pharmaceutical partners and/or to assist existing pharmaceutical partners in techniques for *in vitro* screening of LNA molecules employing the methods of the '199 Patent. Examples of nonpublic documents recently produced by Santaris that show such activity may be found at SANAS00010598; SANAS00011827 at 39-42; SANAS00012607; SANAS00023623; SANAS00117937.

31. On information and belief, in return for the sale of the methods recited in the '199 Patent and the compositions and methods claimed in the '500 and '793 Patents, Santaris received substantial payments from pharmaceutical companies. As evidence of such sales, Santaris recognizes the revenue from the payments in accordance with Santaris's revenue recognition policy, as set forth in Santaris's 2010 Annual Report. Under Santaris's policy, when the significant risk and rewards of ownership of the goods/services have been transferred to the buyer, a sale has occurred and the revenue is booked, *viz*:

> *Revenue comprises product sales and* ***up-front payments***, ***milestone payments***, *and other income associated from research and development contracts. Income is recognized over the period of the agreements in accordance with the terms of the agreements when it is considered realized or realizable and earned.* ***This means that the general income criteria for income recognition has to be met, all significant risk and rewards of ownership of the goods/services has been transferred to the buyer, Santaris Pharma retains neither continuing managerial involvement to the degree usually associated with ownership nor effective control over the goods/services sold****, the amount of revenue can be measured reliably, it is probable that the economic benefit associated with the transaction will flow to the company, and the cost incurred or to be incurred in respect of the transaction can be measured reliably.*

32. In sum, on information and belief, Santaris has engaged in an enterprise of offering for sale and selling to its pharmaceutical company customers drug discovery services and drug candidates that infringe the '199 Patent, the '500 Patent, and/or the '793 Patent, and/or induce infringement of the '199 Patent.

33. 35 U.S.C. § 271(e)(1) ("Section 271(e)(1)") defines a safe harbor against patent infringement:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention…solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

34. This provision entered title 35 in 1984 as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (the "1984 Act"). The House Committee that initiated this provision characterized its limits, noting that the "nature of the interference with the rights of the patent holder" would not be substantial," but "*de minimus* [sic]." H.R. Rep. No. 857, reprinted in 1984 U.S.C.C.A.N. at 2692, 2714 (stating that "all that the generic can do is test the drug for purposes of submitting data to the FDA for approval. Thus, the nature of the interference is *de minimus* [sic].").

35. In 2005, the Supreme Court reaffirmed that not all drug discovery and research under the 1984 Act was subject to the Section 271(e)(1) clinical trial exemption, holding that the exemption may exist where "a drug-maker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is 'reasonably-related' to the 'development and submission of information under . . . federal law.'" *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 207 (2005) (quoting the text of Section 271(e)(1)). Moreover, the Federal Circuit has held that research tools used in drug discovery and development, and are not themselves the subject of regulatory approval, fall outside the protection of Section 271(e)(1). *Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1265 (Fed. Cir. 2008).

36. On information and belief, and as described in the 2010 Annual Report quoted above, Santaris booked millions of dollars of revenue from sales of Isis's patented gapmer antisense technology. On information and belief, these sales are not reasonably related to the development and submission of information to the FDA for regulatory approval, and therefore are not exempted from infringement by the safe harbor provision of 35 U.S.C. § 271(e)(1). Rather, on information and belief, the substantial sums received by Santaris, and the significant future payments contemplated by the Santaris-pharmaceutical company agreements, constitute commercial revenue that Santaris uses to fund and develop its business. In Santaris's 2010 Annual Report, Santaris notes:

> *Since the completion of the Series C round in 2007 the Company has, based on prudent cost management and generation of up-fronts and milestone payments from partners, been able to continue the* ***development of the Company's pipeline, organization and LNA platform****, without any new additional financing*[3]

37. According to Santaris's 2010 Annual report, "In 2010 Santaris Pharma A/S recognized DKK 217.9m in revenues compared to DKK 72.6m in 2009." The revenues are generated in part from Santaris's collaborations with Pfizer, Shire, Glaxo and Enzon (see below) and other commercial activity as alleged herein.

38. On information and belief, Santaris's pharmaceutical industry customers are responsible for development and regulatory approval of drug products. Regardless of whether the pharmaceutical company customers later develop some of the resulting compounds and eventually advance a drug to a phase of development where the Section 271(e)(1) exemption attaches, Santaris's commercial transactions are not themselves related to the generation of data for submission to the FDA. And Santaris's acts of using the patented methods of the '199 Patent in the United States and/or inducing their actual and prospective pharmaceutical partners to screen LNA compounds and/or validate targets in the United States in violation of the '199 Patent are acts not exempt under 35 U.S.C. § 271(e)(1).

[3] Santaris 2010 Annual Report, p. 31.

39. In addition to completed sales and past offers for sale, on information and belief, Santaris continued to offer for sale in the United States the methods claimed in the '199 Patent up to the date of that patent's expiration. On information and belief, Santaris actively pursued transactions with potential customers where it would transfer and/or perform the methods claimed in the '199 Patent for a stated price. These activities undermined the value of the '199 Patent and the Isis platform antisense technology that the patent protects.

40. The following examples of known agreements represent profitable sales by Santaris of technology that infringes the '199, '500 and '739 Patents. Further, Santaris's commercial agreements amount to offers for sale in the United States that depress and harm the value of Isis's patents, as complained of herein. Santaris has built a commercial enterprise that competes with Isis and that depends on the sale, offer for sale, use and importation of Isis's patented technology. Santaris's acts of infringement, as further detailed herein, are inflicting harm on Isis, *inter alia*, in the form of lost or value-diminished licensing opportunities.

THE JANUARY 4, 2011, ANNOUNCED AGREEMENT WITH PFIZER

41. On January 4, 2011, Santaris announced an agreement with Pfizer, Inc. As described in the press release, Pfizer paid Santaris "$14 million for access to Santaris Pharma A/S Locked Nucleic Acid (LNA) Drug Platform to develop RNA-targeted drugs" (the "2011 Pfizer-Santaris Agreement"). (A copy of the Santaris January 4, 2011, press release is attached hereto as Exhibit 4.) As stated in the Santaris 2010 Annual Report, Santaris received $14 million from Pfizer in exchange for access to Santaris's LNA technology, and may receive $600 million in future milestones payments in addition to royalties on sales. Specifically, Pfizer agreed to pay milestones to Santaris upon the identification of up to ten gene targets and the discovery of lead antisense LNA molecule candidates. On information and belief, this agreement represented an expansion of a 2009 agreement with Wyeth in which $7 million was paid to Santaris up front plus a potential $83 million in additional milestone payments. Pfizer acquired Wyeth in 2009 and collectively, the entities are referred to as "Pfizer."

42. On information and belief, and confirming that a sale has occurred, Santaris has recognized as revenue payments from Pfizer and used such revenue for Santaris's commercial purposes.

43. On information and belief, Pfizer is a United States based company, incorporated under the laws of Delaware, and Santaris's offer for sale and sale occurred in the United States. On information and belief, the activity of offering for sale and selling of the Santaris technology in the United States to Pfizer infringed Isis's methods claimed in the '199 Patent, including by, *inter alia*,

- Offering for sale and selling the process of using gapmers to reduce target RNA for target validation purposes; and/or
- Offering for sale and selling the process of screening and identifying gapmer compounds to identify drug candidates for drug development.

44. On information and belief, Santaris further induced Wyeth and/or Pfizer to use, in the United States, Isis's methods claimed in the '199 Patent, knew of the '199 Patent at the time of inducing the acts, and knew that such acts would constitute patent infringement of the '199 Patent in the United States.

45. On information and belief, such activity is not exempt under Section 271(e)(1) because: (a) it constitutes an offer for sale, a sale, use and/or inducing use of a research tool that is not itself the subject of FDA approval; (b) it constitutes an offer for sale, a sale, use and/or inducing use of the methods claimed in the '199 Patent in discovery activity before the trained researcher formed a reasonable basis for believing that a specific compound may work through a particular biological process to produce the particular physiological effect of inhibiting the selected target cell; and/or (c) is a commercial offer for sale, sale, use, and/or inducing use by Santaris that itself is not reasonably related to FDA approval, as further evidenced by Santaris's recognition of revenue from Pfizer.

THE JULY 27, 2006, ANNOUNCED AGREEMENT WITH ENZON

46. On July 27, 2006, Santaris announced an agreement with Enzon Pharmaceuticals, Inc. (the "2006 Enzon-Santaris Agreement"). (A copy of the July 27, 2006, press release is attached hereto as Exhibit 5, and a redacted public version of the Enzon agreement is attached

hereto as Exhibit 6.) On information and belief, Santaris sold two antisense gapmer molecules and targets to Enzon for $6 million. Further, Enzon reimbursed Santaris $2 million for development work, and agreed to pay additional milestones to Santaris upon successful identification of up to six additional targets and for the design, identification, synthesis, screening and selection of an LNA gapmer compound that met certain acceptance criteria. In addition to the upfront payments, Santaris is eligible to collect more than $200 million in development and regulatory milestone payments.

47. On information and belief, subsequent to the execution of the Enzon agreement, and in accordance with its terms, Enzon nominated six additional targets for which Santaris agreed to identify LNA gapmer compounds that inhibit the nominated targets using Isis's methods patented in the '199 Patent and compositions covered in the '500 and '739 Patents. On information and belief, Enzon nominated the beta-catenin and glioma-associated oncogene-2 targets under the 2006 Enzon-Santaris Agreement. Santaris then designed, synthesized, and screened LNA gapmer candidates in order to identify potential drug inhibitors of beta-catenin and glioma-associated oncogene-2 using Isis's methods patented in the '199 Patent and compositions and methods claimed in the '500 and '739 Patents. On information and belief, in 2008, Enzon paid Santaris for successfully delivering candidate molecules for the six additional targets, including beta-catenin. Confirming that a sale occurred, Santaris recognized this revenue and used such revenue for its commercial purposes.

48. Further confirming that a sale occurred, on information and belief, specifically, under the 2006 Enzon-Santaris Agreement, Santaris relinquished rights in "Selected LNA Compounds," including those compounds covered by the '500 and '739 Patents, to sublicense, to develop, import, offer for sale, sell or otherwise commercialize such compounds in the United States. On information and belief, Enzon has "sole ownership, control and responsibility for" regulatory filings in the United States for the candidate molecules acquired from Santaris under the 2006 Enzon-Santaris Agreement.

49. On information and belief, Enzon is an U.S. based company, incorporated under the laws of the State of Delaware, and Santaris's offer for sale and sale to Enzon occurred in the United States.

50. On information and belief, the activity of offering for sale and selling of the Santaris technology in the United States to Enzon infringed Isis's '199 patented methods and the '500 and '739 patented compositions and methods, including by, *inter alia*,

- Offering for sale or selling the process of using gapmers to identify and reduce target RNA for further drug discovery;
- Offering for sale or selling the process of screening and identifying gapmer candidates to identify drug candidates for drug development; and/or
- Selling, offering to sell, and/or importing antisense compounds specific for beta-catenin and/or glioma-associated oncogene-2 in or into the United States.

51. On information and belief, such activity is not exempt under Section 271(e)(1) because: (a) it constitutes an offer for sale, a sale and/or use of a research tool that is not itself the subject of FDA approval; (b) it constitutes an offer for sale, a sale and/or use of the methods claimed in the '199 Patent, and compounds and methods claimed in the '500 and '739 Patents, in discovery activity before the trained researcher formed a reasonable basis for believing that a specific compound may work through a particular biological process to produce the particular physiological effect of inhibiting the selected target cell; and/or (c) is a commercial offer for sale and/or sale that is not reasonably related to FDA approval, as further evidenced by Santaris's recognition of revenue from Enzon.

THE AUGUST 24, 2009, ANNOUNCED AGREEMENT WITH SHIRE PLC

52. On August 24, 2009, Santaris announced an agreement with Shire PLC whereby Santaris would "receive significant upfront payments, milestone payments and royalties for providing access to [Santaris's] LNA technology" and exclusivity for three targets and an additional two targets to be nominated by Shire in the future. Santaris potentially could collect more than $360 million in milestone payments in connection with these five programs. (A copy of the August 24, 2009, Santaris press release is attached hereto as Exhibit 7.) On information

and belief, and confirming a sale has occurred, Santaris has recognized as revenue payments from Shire and used such revenue for Santaris commercial purposes.

53. On information and belief, Shire PLC maintains operations in Cambridge, Massachusetts and Santaris's offer for sale and sale to Shire occurred in the United States. On information and belief, the activity of offering for sale and selling of the Santaris technology in the United States to Shire infringed Isis's methods recited in the '199 Patent, including by, *inter alia*,

- Offering for sale and selling the process of using gapmers to identify and reduce target RNA for further drug discovery; and/or
- Offering for sale and selling the process of screening and identifying gapmer candidates to identify drug candidates for drug development.

54. On information and belief, Santaris further induced Shire and/or its collaborators to use, in the United States, Isis's methods claimed in the '199 Patent, knew of the '199 Patent at the time of inducing the acts, and knew that such acts would constitute patent infringement of the '199 Patent in the United States.

55. On information and belief, such activity is not exempt under Section 271(e)(1) because: (a) it constitutes an offer for sale, a sale, use, or inducing use of a research tool that is not itself the subject of FDA approval; (b) it constitutes an offer for sale, a sale, use, or inducing use of the methods claimed in the '199 Patent in discovery activity before the trained researcher formed a reasonable basis for believing that a specific compound may work through a particular biological process to produce the particular physiological effect of inhibiting the selected target cell; and/or (c) is a commercial offer for sale, sale, use, and/or inducing use by Santaris that itself is not reasonably related to FDA approval, as further evidenced by Santaris's recognition of revenue from Shire.

THE DECEMBER 19, 2007, ANNOUNCED AGREEMENT WITH GLAXOSMITHKLINE

56. On December 19, 2007, Santaris announced an agreement with GlaxoSmithKline ("GSK") whereby Santaris would receive approximately $8 million as an upfront payment, milestone payments, and royalties for providing access to Santaris's LNA technology and exclusivity for four targets. Santaris could potentially collect in excess of $700 million in upfront

and milestone payments under the agreement with GSK. (A copy of the December 19, 2007, Santaris press release is attached hereto as Exhibit 8.)

57. On information and belief, and confirming that a sale has occurred, Santaris has recognized as revenue payments from GSK and used such revenue for Santaris's commercial purposes.

58. On information and belief, GSK maintains operations in Durham, North Carolina and Santaris's offer for sale and sale to GSK occurred in the United States. On information and belief, the activity of offering for sale and selling of the Santaris technology in the United States to GSK infringed Isis's methods recited in the '199 Patent, including by, *inter alia*,

- Offering for sale and selling the process of using gapmers to identify and reduce target RNA for further drug discovery; and/or
- Offering for sale and selling the process of screening and identifying gapmer candidates to identify drug candidates for drug development.

59. On information and belief, such activity is not exempt under Section 271(e)(1) because: (a) it constitutes an offer for sale, a sale and/or use of a research tool that is not itself the subject of FDA approval; (b) it constitutes an offer for sale, a sale and/or use of the methods claimed in the '199 Patent in discovery activity before the trained researcher formed a reasonable basis for believing that a specific compound may work through a particular biological process to produce the particular physiological effect of inhibiting the selected target cell; and/or (c) is a commercial offer for sale and/or sale that is not reasonably related to FDA approval, as further evidenced by Santaris's recognition of revenue from GSK.

FIRST CAUSE OF ACTION
(Infringement of the '199 Patent)

60. Plaintiff realleges and incorporates by reference the allegations contained in paragraphs 1 –59.

61. On information and belief, Santaris has infringed the '199 Patent, pursuant to 35 U.S.C. § 271(a), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the Isis patented methods prior to the expiration of the '199 Patent.

62. On information and belief, Santaris has further infringed the '199 Patent, pursuant to 35 U.S.C. § 271(b), by actively inducing infringement of the '199 Patent in the United States.

63. Plaintiff will be substantially and irreparably harmed if Santaris is not enjoined from infringing the '199 Patent.

64. Santaris's infringement is willful.

65. Plaintiff has been injured by Santaris's infringement.

66. This case is exceptional, and Plaintiff is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

SECOND CAUSE OF ACTION
(Infringement of the '500 Patent)

67. Plaintiff realleges and incorporates by reference the allegations contained in paragraphs 1 – 59.

68. On information and belief, Santaris has infringed the '500 Patent, pursuant to 35 U.S.C. § 271(a), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the claimed compositions and methods prior to the expiration of the '500 Patent.

69. Plaintiff will be substantially and irreparably harmed if Santaris is not enjoined from infringing the '500 Patent.

70. Santaris's infringement is willful.

71. Plaintiff has been injured by Santaris's infringement.

72. This case is exceptional, and Plaintiff is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

THIRD CAUSE OF ACTION
(Infringement of the '739 Patent)

73. Plaintiff realleges and incorporates by reference the allegations contained in paragraphs 1 – 59.

74. On information and belief, Santaris has infringed the '739 Patent, pursuant to 35 U.S.C. § 271(a), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the claimed compositions and methods prior to the expiration of the '739 Patent.

75. Plaintiff will be substantially and irreparably harmed if Santaris is not enjoined from infringing the '739 Patent.

76. Santaris's infringement is willful.

77. Plaintiff has been injured by Santaris's infringement.

78. This case is exceptional, and Plaintiff is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Isis prays for judgment against Defendants, Santaris Pharma A/S Corp. and Santaris Pharma A/S, and respectfully requests the following relief:

1. A judgment that the '199, '500 and '739 Patents have been infringed by Santaris;

2. A judgment for a permanent injunction enjoining Santaris, its officers, agents, servants, employees, and those persons acting in active concert or participation with all or any of them from manufacturing, using, offering to sell, selling, or importing into the United States Isis's methods or products prior to the expiration of the '199, '500 and/or '739 Patents, except as to such activities, if any, within the scope of 35 U.S.C. § 271(e)(1);

3. An award of damages together with interest, and a judgment that the damages so adjudged be trebled pursuant to 35 U.S.C. §§ 283 and 284;

4. A judgment that this is an exceptional case and that Plaintiff be awarded its attorneys' fees incurred in this action pursuant to 35 U.S.C. § 285;

5. Costs and expenses in this action; and

6. Such other and further relief as the Court deems just and appropriate.

Dated: April 25, 2013

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

By: */s/ William G. Gaede, III*
William G. Gaede, III

Attorneys for Isis Pharmaceuticals, Inc.

DEMAND FOR JURY TRIAL

Plaintiff respectfully requests a jury trial on all issues triable thereby.

Dated: April 25, 2013

MCDERMOTT WILL & EMERY LLP

By: */s/ William G. Gaede, III*
William G. Gaede, III

Attorneys for Isis Pharmaceuticals, Inc.